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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/505,239	10/12/2004	Nadya I Tarasova	229694	1908

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EXAMINER	
CORDERO GARCIA, MARCELA M	
ART UNIT	PAPER NUMBER
1654	
MAIL DATE	DELIVERY MODE
06/23/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/505,239	TARASOVA ET AL.	
	Examiner	Art Unit	
	MARCELA M. CORDERO GARCIA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *5,19,53,68-71,76-81,86,87,89,112-113, 116-117, 120, 122,124, 126* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 6, 14-17, 20, 28, 49-51, 54, 62-64, 67, 88, 90, 98, 110, 121, 123, 125, 127* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-3,5,6,14-17,19,20,28,49-51,53,54,62-64,67-71,76-81,86-90,98,110,112,113,116,117 and 120-127.

DETAILED ACTION

This Office Action is in response to the replies received on 30 July 2007 and 14 January 2008.

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1654, Examiner Marcela M Cordero Garcia.

Claims 1-3, 5, 6, 14-17, 19, 20, 28, 49-51, 53, 54, 62-64, 67-71, 76-81, 86-90, 98, 110, 112, 113, 116, 117 are pending in the application. Claims 1, 5, 6, 15, 19-20, 49, 53-54, 88-90 have been amended by Applicant. Claims 120-127 are new claims. Claims 5, 19, 53, 68-71, 76-81, 86, 87, 89, 112-113, 116-117 have been previously withdrawn. Newly submitted claims 120, 122,124, 126 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: they depend upon previously withdrawn claims. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 120, 122,124, 126 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 6, 14-17, 20, 28, 49-51, 54, 62-64, 67, 88, 90, 98, 110, 121, 123, 125, 127 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons set forth in the previous Office Action.

Applicant's arguments

The Office Action alleges the scope of the original claims is overly broad with respect to the "ligand" and "cytotoxic agent" elements, and that the description of the specification does not provide adequate support for the breadth of the claims. Applicants disagree with the rejection as it was applied to the original claims. One of ordinary skill in the art reading the application, together with the knowledge available in the art aa the time of filing, would readily ascertain that Applicants were in possession of the full scope of the claimed subject matter as of the filing date. Nevertheless, in the interest of expediting the prosecution of this application, Applicants have amended the claims.

As amended, the claims are directed to a conjugate comprising a ligand, one of several defined linkers, and a cytotoxic agent, wherein the ligand specifically binds to a gastrin (CCKB) receptor. Each element of the claims is described in the present application in a manner consistent with Section 112.

With respect to the ligand, the gastrin (CCKB) receptor was well-characterized and known to those of ordinary skill in the art as of the filing date, as were ligands to the receptor. Thus, a ligand that binds the gastrin receptor need not be described in detail in order to meet the requirements of section 112. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986); see also

Capon v. Eshhar, 418 F.3d 1349, 1357, 76 USPQ2d 1078, 1085 (Fed. Cir. 2005). Nevertheless, several species of ligands that bind a gastrin (CCKB) receptor are disclosed in the present application and recited in dependent claims (e.g., [0015]-[0016] and claims 5, 6, 19, 20, 53, 54, 89 and 90).

With respect to the linker, each claim recites the sequence of the linker motif with particularity. Thus, there should be no issue as to the written description of this element.

As for the cytotoxic agent, the claims are not limited to any particular cytotoxic agent. Cytotoxic agents were commonplace at the time the invention was filed. Furthermore, the examples provide specific guidance as to the use of a variety of different cytotoxic agents. Given the description provided in the present application, those of ordinary skill in the art would have appreciated that a variety of cytotoxic agents could be linked to the linker motif and used in the invention.

In view of the foregoing, Applicants believe that the claimed subject matter is adequately described such that one of ordinary skill in the art would be on notice that Applicants were in possession of the full scope of the claimed subject matter at the time of filing. Accordingly, Applicants respectfully request that the Section 112 rejection of the claims as lacking written description be withdrawn.

Response to Arguments

Applicants' arguments filed 30 July 2007 have been fully considered but they are not persuasive for the reasons of record and because the term "ligand that specifically binds to a gastrin (cholecystokinin B (CCKB)) receptor" is a functional term, not drawn to any specific core and that is not adequately represented in the examples / disclosure.

The disclosure teaches at [0013] that, with respect to the present invention, that "[t]he ligand can be a peptide or a peptidomimetic. Desirably, the ligand comprises a functional group that can be attached to a linker and the attachment of the ligand to a linker does not eradicate the ability of the ligand to bind specifically to a cell-surface receptor. The term "peptide" as used herein means any polyamide that comprises two or more amino acids covalently linked by an amide bond between the carboxylic acid group of one and the alpha amino group of the other. It is generally appreciated by one skilled in the art that a peptide can optionally be glycosylated, amidated, carboxylated, phosphorylated, esterified, N-acetylated, or converted into an acid addition salt and/or optionally dimerized or polymerized. With respect to the present invention, the peptides are generally amidated unless otherwise indicated. The term "peptidomimetic" as used herein refers to a compound containing non-peptidic structural elements that is capable of mimicking or antagonizing the biological action(s) of a natural parent peptide. One skilled in the art will appreciate that a peptidomimetic does not have classical peptide characteristics, such as enzymatically scissile peptidic bonds. In one embodiment of the present invention, the peptidomimetic is a peptoid. The term "peptoid" as used herein refers to a peptidomimetic that results from the oligomeric assembly of N-substituted glycines. For example, CI-988, (see Augelli-Szafran et al., Bioorg. Med. Chem. 4: 1733-1745 (1996)), which has a carboxyl group (see arrow below) for attachment to a linker, can be a peptoid ligand of the conjugate of the present invention."

By the same token: the disclosure at [0020] teaches that "[t]he cytotoxic agent in the conjugate can be any agent known in the art but, preferably, the cytotoxic agent is

cemadotin, a derivative of cemadotin, a derivative of hemiasterlin, esperamicin C, neocarzinostatin, maytansinoid DM1,7-chloromethyl-10,11 methylenedioxy-camptothecin, rhizoxin, or the halichondrin B analog ER-086526. The term "derivative" as used herein refers to a molecule that contains the same backbone structure of the parent molecule but is modified to some extent in the side-chains of the molecule."

The Examples provided are as follows: Example 1: cemadotin-peptide conjugates VLALAEEEAYGW(Nle)DF and FLALAEEEAYGW(Nle)DF. Example 2: conjugates comprising the hemiasterlin derivative, SPA 110, conjugated to VLALAEEEAYGW(Nle)DF-NH2. Example 3 describes the activity of the hemiasterlin derivative, SPA 110, the linker VLALA and the gastrin decapeptide, which was determined to be low activity apparently due to insufficient processing of the conjugate in the lysosomes. Example 4 is drawn to the generation of a library of hemiasterlin derivatives with extended by one α-amino acid at the C-terminus and their activity. Please note that the variable R_2 does not appear to be defined. Example 5 is drawn to the generation of a library of hemiasterlin derivatives extended by two α-amino acids at the C-terminus and their activity. Please note that the variable R_2 does not appear to be defined. Example 6 is drawn to an example describing a variety of cytotoxic agents that *can be used* as conjugates of the present invention and illustrates the point at which the ligand-linker fused sequence is attached to the cytotoxic agents The cytotoxic agents described are rhizosin, HTI-286, esperamycin, ER-086526, cemadotin, DM1 and 10,11-methylenedioxy-camptothecin. Example 7 is drawn to an example that demonstrates an assay to test the cytotoxicity of the conjugates in vitro and demonstrates that

administration of a conjugate, which comprises a ligand that specifically binds to gastrin receptor in isogenic cell lines, one transfected with the target cell surface receptor and the parent cell line without detectable receptor expression. Transfection of NIH/3T3, CHO and HeLa cells with gastrin receptor cDNA. Table 1 shows a dose-dependent decrease in the survival of only cells that expressed the gastrin receptor. Please note that the conjugates used were not identified. Example 8 is drawn to an assay to test the cytotoxicity of the conjugates in vivo. Briefly drug conjugates are injected into grafted tumors obtained from mice. Please note that the conjugates were not identified.

After careful consideration it is therefore deemed that the inventors did not have possession of the invention as claimed at the time the invention was made, and which encompassed any ligand binding the CCKB receptor, including peptidomimetics, peptoids and peptides defined by their functional activity and not drawn to a specific sequence or structure, and in addition encompassing conjugated cytotoxic drugs and derivatives thereof beyond the few exemplified in the disclosure. Therefore the written description rejection is maintained.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCELA M. CORDERO GARCIA whose telephone number is (571)272-2939. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cecilia Tsang/
Supervisory Patent Examiner, Art Unit 4131

/Marcela M Cordero Garcia/
Examiner, Art Unit 1654